Original Article

Cluster analysis of symptoms of Bangladeshi women with breast cancer in palliative care centre of a tertiary hospital

Alam S[1], Ahmad N[2], Bhuiyan MZR[3], Sarmin S[4], Shams MJ[5], Rashid MU[6]

Abstract

Breast cancer patients may experience multiple symptoms due to the disease itself, treatment or combination of both. The aim of the present study was to identify group of symptoms experienced by the patients with breast cancer using cluster analysis. We examined symptom profiles of 120 patients with breast cancer who attended a hospital palliative care centre in a tertiary institution. Following symptoms were analyzed: pain, nausea, loss of appetite, constipation, weakness, cough, breathlessness, sleeplessness, lymphedema, sadness, anxiety and depression. Hierarchical cluster analysis was used to identify the natural groupings within the set. We could identify three clusters. Cluster 1 was characterized by pain, depression, anxiety, weakness, sleeplessness and loss of appetite. Cluster 2 comprised of cough, breathlessness, nausea and constipation. Cluster 3 consisted of two symptoms lymphedema and sadness. The results revealed that the patients with breast cancer experienced symptoms that are multiple and clustered together. Neuro-psychiatric symptoms and weakness formed a significant strong relationship. Knowledge obtained from this study can be beneficial for better understanding, assessment and management of symptom clusters in women with breast cancer. It may also help patients to plan ahead for them to seek management of concurrent symptoms to improve their quality of life.

Key words: Breast cancer, cluster analysis, palliative care

Introduction

Worldwide breast cancer (BC) is the most common cancer of women.[1] BC is also the most common cancer in Bangladesh.[2] BC patients may experience multiple symptoms at a time due to the disease itself, treatment or combination of both.[3] The study follows definitions of 'symptoms' and 'clustered symptoms' after a literature review. Subjective perception of disease is known as "symptom".[1,2] Symptoms may be complex and clustered in nature.[3] Aggregations of three or more symptoms that may or may not be originated from a single source are known as "clustered symptoms". Sufferings due to multiple symptoms are a source of reduced quality of life and functional status in patients with breast cancer. Previous studies have found that symptoms of fatigue, depression, sleep disturbances and pain are prevalent across different stages of breast cancer and treatment.[2,4-8]

Symptoms such as pain, fatigue, sleep alterations, depression, loss of appetite were identified by previous studies as most common, associated or highly prevalent symptoms of breast cancer patients.[1,8] Symptom clusters may affect each other and may trigger other symptoms to affect QOL.[3,9,10] Identification of meaningful subgroups of patients within this disease/particular to the disease is therefore important as these groups may represent different aetiological and pathophysiological entities and they may require different treatment approaches.[9-11] Symptom clusters in Bangladeshi women with breast cancer are little known. The aim of this study was to investigate the existence of natural symptom clusters of women with breast cancer systematically.

Methods

This was a retrospective observational study. Hospital notes and case sheets were screened to identify patients with breast cancer primary breast cancer patients registered with the Centre for Palliative Care (CPC) over a five-year period between January 2009 and December 2013), in the only medical university in Bangladesh to include in the study. The inclusion criteria were women aged 18 years or above diagnosed with breast cancer of any stage with or without ongoing definitive treatment. Exclusion criteria included a past medical history of cancer or immune-related disease (*i.e.* multiple sclerosis, HIV, lupus) or not having a histopathologically confirmed breast malignancy.

At the time of first consultation patients demographic and

1. Professor Dr Sarwar Alam, Professor, Department of Oncology, BSMMU, Dhaka
2. Professor Dr Nezamuddin Ahmad, Professor of Palliative Medicine, Department of Medicine (Palliative care wing), BSMMU, Dhaka
3. *Dr Md Zillur Rahman Bhuiyan, Assistant Professor, Department of Oncology, BSMMU, Dhaka.
4. Dr Sadia Sharmin, Assistant Professor, Department of Oncology, BSMMU, Dhaka
5. Dr Mohammad Jahan Shams, Medical Officer Department of Oncology, BSMMU, Dhaka.
6. Dr Mamun Ur Rashid, Medical Officer, Department of Oncology, BSMMU, Dhaka.

**For correspondence*

other symptoms were documented after thorough assessment of the patient in a case sheet with a total of 91 variables (22 demographic and 69 clinical) by a team that include one medical doctor with six weeks training in palliative medicine and one nurse trained in six weeks palliative nursing. The university institutional review board approved this study.

Analyses were carried out using SPSS. Baseline data were analyzed using parametric statistics and are expressed as mean values. Pearson correlation coefficients were used to explore linear relationships between different continuous variables.

A hierarchical cluster analysis was used to classify data based on variables according to physical and psychological symptoms. This method is explanatory and we had no preconceived ideas about how variables would cluster together. Euclidean distance measure was used in the process. Similar symptoms were put by the technique into the same group in a hierarchical way, so that most similar two symptoms are first put into a group. The algorithm iteratively estimates the cluster means and assigns each variable to the cluster. The validity of the three subgroups solution was explored by comparing subgroup membership across physical and psychological symptom measures, using ANOVA. Significance was defined as $p<0.05$.

Results

A total of 120 case sheets of carcinoma breast patients were selected for this study. Among those case sheets 8 were discarded because the patients did not have any histopathological evidence on admission. These patients underwent FNAC after admission to have diagnosis. Data are therefore presented on 112 patients. There was no significant difference in baseline measures of physical, psychological symptoms or demographic variables between those patients whose case sheets were discarded for this study. The initial dataset included 120 subjects ranging in age from 17 to 80 years. Complementary therapy was taken by 40 (35.7) patients, which include Ayurveda, homeopathy or religious approach. Among the patients, 93 (83%) of the patients had definitive therapy. Forty-seven patients (44%) had emotional problems. The most common conditions were depression, n=28 (28%) and anxiety states, n=32 (30%).

Time since diagnosis to first consultation ranged from 3 days to 143 months, with a mean of 25 months (SD=25.3). Time since diagnosis to death ranged from 8 days to 145 months, with a mean of 28 months (SD=27.67). Almost 39 percent of the women had breast cancer stage II or over with a missing value of 37.5%. Other clinical characteristics are summarized in Table-I & Table-II.

Table - I: Patient characteristics (n=112)

Patients	N (%)
18-39 years	39 (34.8)
40-59 years	58 (51.8)
60 and above	15 (13.4)
Median (Minimum-Maximum)	45 (30-75)
ECOG Performance Status	
Stage 1	24 (21.4)
Stage 2	9 (8)
Stage 3	19 (17)
Stage 4	15 (13.4)
Time of Diagnosis - First oncological consultation	
<12 months	35 (31.5)
12 – 60 months	59 (53.1)
>60 months	8 (7.2)
Time of Diagnosis - Death	
<12 months	21 (18.9)
12-60 months	27 (24.3)
>60 months	4 (3.6)

Table - II: Frequency of individual symptoms (n=112)

Symptoms	n	%
Pain	86	76.8
Nausea	33	29.5
Loss of appetite	42	37.5
Constipation	29	25.9
Weakness	48	42.9
Cough	25	22.3
Breathlessness	30	26.8
Sleeplessness	41	36.6
Lymphoedema	51	45.5
Anxiety	47	42.0
Depression	24	21.4
Sadness	29	25.9

Significant medium correlation between pain with weakness and anxiety, large correlation between nausea with loss of appetite and a large correlation was found with weakness and sleeplessness. Other significant correlations are shown in table - III.

Table-III : Correlation among different symptoms

Pain	Nausea	Loss of appetite	Consti pation	Weak ness	Cough	Breath lessness	Sleepless ness	Anxiety	Depr ession	Sadness
	.22 (.02)	.25 (.008)	.18 (.05)	.35 (.001)			.24 (.01)	.33 (.001)	.18 (.05)	.22 (.01)
Nausea		.51 (.001)			.21 (.02)	.18 (.05)	.24 (.01)	.20 (.03)		.19 (.03)
Loss of appetite			.25 (.006)	.34 (.001)			.33 (.001)	.19 (.03)	.18 (.05)	
Constipation							.23 (.001)			.30 (.001)
Weakness					.23 (.01)	.29 (.002)	.43 (.001)		.21 (.02)	

Hierarchical cluster analysis grouped together related symptoms, based on the observed similarities between them. Using the agglomerative cluster approach, a dendrogram was generated. Figure-1 shows the total process of joining individual points to one big cluster.

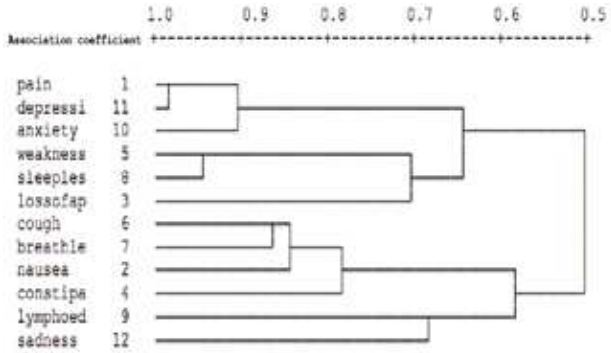

Figure -1: *Results of cluster analysis*

The results of cluster analysis with matrix of association coefficients between individual symptoms are shown in Table 3. Pain, depression and anxiety were associated most closely. The association coefficient between pain and depression, anxiety and weakness was .917, .875 and .708. Furthermore, weakness and sleeplessness formed a relatively tight cluster with a distance of .875. Loss of appetite was joined next to this cluster, with an association coefficient of .625. The next symptoms included in this cluster were cough, breathlessness, nausea and constipation. Thus we could identify three symptom clusters. Cluster 1 was characterized by pain, depression, anxiety, weakness, sleeplessness and loss of appetite. This cluster was named as "neuro-psychiatric' symptom cluster. The symptoms in cluster 2 comprised cough, breathlessness, nausea and constipation. This cluster was named as 'respiratory-gastrointestinal' symptom cluster. Cluster 3 consisted of two symptoms lymphedema and sadness and this was named as 'miscellaneous' symptom cluster.

A one-way between-groups multivariate analysis of variance was performed to investigate cluster differences in physical and psychological symptoms. Pain, nausea, loss of appetite, constipation, weakness, cough, breathlessness, sleeplessness, lymphoedema, anxiety, depression and sadness were used as dependent variables. The independent variable was group containing three clusters. Preliminary assumption testing was conducted to check for normality, linearity, univariate and multivariate outliers, homogeneity of variance-covariance matrices, multicollinearity, with no serious violations noted. There was a statistically significant difference between group 1, group 2 and group 3 on the combined dependent variables, F (11, 11) = 2.76, p = .011; Wilks' Lambda = .07; partial eta squared = .95. When the results for the dependent variables were considered separately, differences to reach statistical significance, using a Bonferroni adjusted alpha levels of .302, .412 and .20, was weakness, F (2, 21) = 5.98, p = .009, partial eta squared = .36; sleeplessness F (2, 21) = 9.05, p = .001, partial eta squared = .46 and lymphedema F (2, 21) = 4.00, p = .03, partial eta squared = .27. An inspection of the mean pain scores indicated that cluster 1 had slightly lower levels of pain ($C1$ = .78, SD = .44) than other two groups ($C2$ = 1.00, SD = .00) & ($C3$ = 1.00, SD = .00). (Table-IV)

Table-IV: Results of cluster analysis: matrix of association coefficients between individual symptoms

	Pain	Depression	Anxiety	Weak-ness	Sleepless-ness	Loss of appetite	Cough	Breath-lessness	Nausea	Consti-pation	Lymph-oedema	Sadness
pain		0.917	0.875	0.708	0.583	0.625	0.25	0.292	0.417	0.458	0.5	0.5
Depression	0.92		0.792	0.625	0.5	0.542	0.167	0.208	0.333	0.375	0.583	0.583
Anxiety	0.88	0.792		0.583	0.458	0.667	0.292	0.333	0.458	0.5	0.458	0.458
Weakness	0.71	0.625	0.583		0.875	0.667	0.458	0.583	0.458	0.583	0.375	0.375
Sleeplessness	0.58	0.5	0.458	0.875		0.625	0.583	0.542	0.5	0.542	0.333	0.333
Loss of appetite	0.63	0.542	0.667	0.667	0.625		0.542	0.583	0.625	0.667	0.375	0.375
Cough	0.25	0.167	0.292	0.458	0.583	0.542		0.792	0.75	0.792	0.417	0.417
Breathlessness	0.29	0.208	0.333	0.583	0.542	0.583	0.792		0.792	0.75	0.458	0.458
Nausea	0.42	0.333	0.458	0.458	0.5	0.625	0.75	0.792		0.625	0.583	0.583
Constipation	0.46	0.375	0.5	0.583	0.542	0.667	0.792	0.75	0.625		0.375	0.375
Lymphoedema	0.5	0.583	0.458	0.375	0.333	0.375	0.417	0.458	0.583	0.375		
Sadness	0.46	0.375	0.5	0.417	0.458	0.5	0.625	0.583	0.708	0.5	0.625	0.625

Discussion

There are several important findings derived from this retrospective analysis that may be used to inform future studies. We chose a set of symptom clusters of pain, nausea, loss of appetite, constipation, weakness, cough, breathlessness, sleeplessness, lymphedema, sadness, anxiety and depression based on previous literature. Denieffe et al undertook a prospective longitudinal study to discover the symptoms of breast cancer before surgical intervention and also to know the impact of these symptoms on ninety four patients.[9,11-16] It was found that 35% of the females with BC had pain, 32% had fatigue, sleep disturbances affected 25.5% and 11% had depression. Quality of life was measured with Hospital Anxiety and Depression Scale, Insomnia Severity Index, Functional Assessment of Cancer Therapy-Fatigue; and Brief Pain Inventory and European Organization for research and treatment. Fatigue showed a moderate correlation with emotional functioning and a weak correlation with physical and social functioning. A secondary analysis of 128 women with breast cancer (Stages I- II) was undertaken at 4 weeks after lumpectomy or mastectomy, before receiving their first dose of chemotherapy. This time point was selected because it provided an adequate duration of time after surgery for return of baseline immune parameters. They chose a well-described symptom cluster of fatigue, depression, pain and sleep disturbance, a majority of the sample had very low symptom scores for both pain and sleep disturbances. In our study, about 77 (68.8%) of the participants had undergone surgery, 88 (78.6%) had completed or undergoing chemotherapy schedules and 60 (53.6%) had radiotherapy. We found that pain (76.8%) had the highest scores among all symptoms.

We excluded symptoms with extremely low scores. Although pain was measured with the numerical scale, other symptoms were not measured with any measurement scale. Therefore we could not assign any clinical significant cut-off score for each symptom, however we decided to include the symptoms according to their scores to increase the homogeneity of the sample in terms of their symptom experience. We decided to include symptoms which had scores >20%.

Another study with a total of 320 women with breast cancer undergoing chemotherapy were ranged in age from 17 to 68 years, with a mean of 47.3 years (SD= 8.8), majority had stage II breast cancer.[17-20] This study revealed that symptom clusters were not identical across symptom dimensions. In addition, symptom clusters revealed in this study are more likely treatment-related symptom clusters, particularly gastrointestinal and fatigue related symptoms. Gastrointestinal symptoms (such as nausea, vomiting, lack of appetite) and fatigue related symptoms were reported as common adverse effects of the standard chemotherapy regimen using the combination of cyclophosphamide, methotrexate, 5-FU, and doxorubicin. Gastrointestinal and

fatigue are identified as clusters in breast cancer patients undergoing chemotherapy in two studies.[21-24] Our study identified neuro-psychiatric and weakness as clusters in breast cancer patients. The findings from this study supported previous studies that symptom clusters existed in this group of women across cultural studies. The differences in the structures of symptom clustering might be from the differences between the sample characteristics or the methodology used in each study.

There are three major limitations of the study. Firstly, approximately 40% of the case sheets did not include ECOG measurements. Although they appeared similar to those who had ECOG grades in terms of gastrointestinal symptoms and psychological profile, subtle differences cannot be excluded. Secondly, the study was carried out in a tertiary centre and therefore the finding should not be generalized to primary care or community subjects with carcinoma breast. Thirdly, all the symptoms were not measured using reliable and validated scales. The drawback of this is that we have failed to recognize clinical details that might be added to the research. The way forward may be to target to develop specific treatments for subgroups.

The current study provided empirical evidence that Bangladeshi breast cancer patients experience multiple symptom clusters. Future study could be done to verify these three symptom clusters and identify underlying mechanism. The findings suggested that these women experienced multidimensional symptoms together that were interrelated and aggregated in three major groups. Health professionals could pay more attention to more specific assessment and management to these patients.

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